REMARKS

This paper is directed to the May 27, 2005 Office Action and it also follows the personal interview held on June 29, 2005. Entry of the above listing and claim amendments is respectfully requested since this paper (Amendment Under 37 C.F.R. §1.116) either places the application in condition for allowance or reduces issues if an appeal becomes necessary.

After implementing the above claim listing, the status of the claims in this application will be as follows:[1]

I. Status of Claims After Entry

After entry of the claims identified in the complete listing above, the status of the claims will be as follows:

Amended claims: 1436-1439 and 1441-1442.

Canceled claims: 1500-1503

New claims added: None

Pending claims presented for further examination: 569-571, 573-575, 577, 582-589, 592-594, 597-600, 602-604, 607-608, 610-612, 614-624, 634-635, 637-638, 641-642, 646, 648-651, 656-661, 667, 670, 707-714, 716-717, 719-723, 725-727, 729, 734-747, 749-752, 754-756, 759-760, 762-764, 766-776, 786-787, 789-790, 793-794, 796-797, 800-803, 808-813, 819, 822, 859-866, 868-869, 871-875, 877-879, 881, 886-899, 901-904, 906-908, 911-912, 914-916, 918-928, 938-939, 941-942, 945-949, 952-955, 960-965, 971, 974, 1011-1018, 1020-1021, 1023-1027, 1029-1031, 1033, 1038-1051, 1053-1056, 1058-1060, 1063-1064, 1066-1068, 1070-1080, 1090-1091, 1093-1094, 1097-1099, 1101, 1104-1107, 1112-1117, 1123, 1126, 1163-1170, 1172-1173, 1175-1179, 1181-1183, 1185, 1190-1200, 1204, 1208-1209, 1212-1216, 1218-1244, 1248-1249, 1253, 1255-1258, 1263-1270, 1272, 1275, 1278-1294, 1296-1328, 1331-1332, 1334-1351, 1353-1354, 1357-1358, 1360, 1362-1369, 1372-1380, 1383, 1386-1391, 1393-1407, 1409-1487, 1490-1491, 1493-

[1] **Applicants are grateful that many of the claims have been allowed as represented by Item #5 in the May 25, 2005 Office Action.**

1499, 1504-1516, 1518, 1520-1525, 1527, 1530-1539, 1541, 1544-1568, 1570-1585, 1587, 1592-1612, 1614-1615, 1618-1621, 1623-1628, 1631-1632, 1635-1647, 1649-1656, 1658, 1660-1667, 1670-1677, 1679-1680, 1682, 1685-1773 and 1775-1796.

II. Claim Changes

A. Claim Cancellations

As discussed at the June 29, 2005 interview, Applicants have canceled claims 1500-1503. These claims had been rejected in the May 25, 2005 Office Action for NEW MATTER directed to the chemical linkages specified as an olefinic bond, various amines, etc. to other nucleotide or nucleotide analog structures other than attaching a Sig moiety to a BASE moiety. See pages 4-5 of the May 25, 2005 Office Action.

B. Claim Amendments

Claims 1436-1439 and 1441-1442 have each been amended in an effort to define Applicants' invention more clearly. These claims had also been rejected for vagueness and indefiniteness in the May 25, 2005 Office Action (pages 7-8) for setting forth without clear antecedent basis the phrase "said nucleotide structure or nucleotide analog structure (i)." This matter including the new claim language was also discussed at the June 29, 2005 interview.

It is believed that none of the foregoing amendments to the claims raises any issue of new matter. Entry of these claim amendments and the claim cancellations is respectfully requested.

Before addressing the issues that were discussed at the June 29, 2005 interview, Applicants wish to express their gratitude for the courtesy and time extended by Examiners Ardin H. Marschel and Michael Woodward to Applicants' representative, Eugene C. Rzucidlo, Esq. of the law firm,

Greenberg Traurig, Robert M. Schulman, Esq. of the law firm, Hunton & Williams, and their undersigned attorney.

III. Substance of the June 25, 2005 Interview

Several matters were discussed at the June 25, 2005 interview.

A. Missing Substance of the September 21, 2004 Inteview (May 25, 2005 Office Action, Page 4)

The first matter discussed at the June 29, 2005 interview was Applicants' missing substance of the April 1, 2004 interview. At the June 29, 2005 interview, Applicants' attorney presented a paper titled "Substance of the April 1, 2004 Interview" and designated as Exhibit 1 (3 pages). It was indicated that the remarks contained in this paper were culled from Applicants' July 13, 2004 Supplemental Amendment. The substance was made of record in the application. For the sake of completeness, a copy of Applicants' Substance of the April 1, 2004 Interview (Exhibit 1) is submitted with this paper, also as Exhibit 1.

B. New Matter Rejection

1) claims 1500-1503 directed to linkages of Sig attached to phosphate and sugar (May 25, 2005 Office Action, Pages 4-5)

At the June 25, 2005 interview, Applicants' attorney presented a paper designated Exhibit 2 (3 pages) in which the cancellation of claims 1500-1503 was offered and briefly discussed. Exhibit 2 was made of record in the application.

2) claims 1723-1724, 1740-1741, 1769-1773, 1775 & 1796 directed to different or same indicator molecules (pages 5-7)

The matter of the "same or different indicator molecules" was discussed next at the June 25, 2005 interview. Applicants' attorney presented a list of the claims directed to different or same indicator molecules that had been rejected in the May 25, 2005 Office Action. The list was designated Exhibit 3 (3 pages) and was made of record. Applicants' representative pointed to several portions in the '069 specification that support the use of different or same indicator

molecules in several disclosed processes including nucleic acid detection and chromosomal karyotyping. The representative indicated that the '069 specification generally describes using modified nucleotides and modified nucleotide analogs for dectection/identification of nucleic acid-containing etiological agents, screening bacteria for antibiotic resistance, diagnosis of genetic disorders, chromosomal karyotyping and the identification of tumor cells, citing the last paragraph on page 6. With respect to nucleic acid sequencing, reference was made to the second paragraph on page 84 which describes the use of self-signaling molecules "to monitor any nucleic acid hybridization reaction" and its importance "for detecting nucleic acids in gels (for example, sequencing gels). Thus, as explained at the June 29, 2005 interview, nucleic acid sequencing is just another form of nucleic acid detection.

Regarding the use of different indicators, the representative referred to Example 9 which is titled "Use of Labeled DNA Sequences" and which contains three sub-examples, including karyotyping, the diagnosis of genetic disorders and microorganism detection and identification. Portions were cited from the two sub-examples in Example 9 that deal with karyotyping and genetic disorder diagnosis. According to the representative, these two sub-examples describe the use of different colored fluorescent dyes and different colored labels. From a reading of the '069 disclosure and the first two parts of Example 9, the use of such different colored fluorescent dyes and different colored labels in other uses, such as nucleic acid detection which is described in the last part of Example 9, and nucleic acid sequencing, another form of nucleic acid detection, would have been reasonably conveyed.

The Examiners responded by suggesting that these points should be presented in Applicants' next response for consideration.

C. Vagueness and Indefiniteness

The vagueness and indefiniteness rejection of claims 1436-1439 and 1441-1444 was discussed next. Applicants' attorney presented some proposed amendments in the form of Exhibit 4 (2 pages) which were made of record. A suggestion was made by the Examiner(s) to recite in the rejected dependent claims that the attachment is via a covalent attachment which might provide a better antecedent basis. Applicants' attorney noted the suggestion.

IV. May 25, 2005 Office Action

A. Missing Interview Summary

As indicated above, a Substance of the April 1, 2004 Interview is being submitted herewith as Exhibit 1.

B. Rejection Under 35 U.S.C. §112, First Paragraph (New Matter)

Claims 1500-1503, 1723-1724, 1740-1741, 1769-1773, 1775 and 1796 stand rejected for new matter under 35 U.S.C. §112, first paragraph. The text of the rejection is set forth on pages 4-7) in the Office Action.

1. New matter rejection of claims 1500-1503 directed to chemical linkages to other nucleotide or nucleotide analog structure other than attaching a Sig moiety to a BASE moiety

As noted above and as discussed at the June 29, 2005 interview, Applicants have canceled claims 1500-1503, thus rendering moot the new matter rejection applied to these claims. Reconsideration and withdrawal of this ground of rejection is respectfully requested.

2. New matter rejection of claims 1723-1724, 1740-1741, 1769-1773, 1775-1776 & 1796 directed to different or same indicator molecules

Applicants believe that the use of different or same indicator molecules in nucleic acid sequencing processes would have been reasonably conveyed to a person skilled in the art from a reading of the '069 specification.

Karyotyping, nucleic acid detection and nucleic acid sequencing are all disclosed uses in the '069 specification of Applicants' probes and self-signaling molecules.

At the outset, Applicants are mindful that the '069 specification discloses the use of detectable non-radioactively labeled nucleotides, nucleotide analogs and nucleic acid fragments in a number of different processes. In fact, the '069 specification makes no special mention of using

these inventive features in one process to the exclusion of others. For example, the last two paragraphs on page 6 in the '069 specification disclose:

> ***Nucleotides modified in accordance with the practices of this invention and oligo- and polynucleotides into which the modified nucleotides have been incorporated may be used as probes in biomedical research, clinical diagnosis, and recombinant DNA technology.*** These various utilities are based upon the ability of the molecules to form stable complexes with polypeptides which in turn can be detected, either by means of properties inherent in the polypeptide or by means of detectable moieties which are attached to, or which interact with, the polypeptide.
>
> ***Some uses*** include ***detecting and identifying nucleic acid-containing etiological agents,*** e.g. bacteria and viruses; ***screening bacteria for antibiotic resistance; diagnosing genetic disorders,*** e.g. ***thalassemia and sickle cell anemia; chromosomal karyotyping;*** and ***identifying tumor cells.***[2] **[emphasis added]**

Thus, the '069 specification clearly conveys that Applicants' probes are for use in the diverse fields of biomedical research, clinical diagnosis and recombinant DNA technology, and that more specific uses include:

- nucleic acid detection/identification
- antibiotic resistance screening in bacteria
- genetic disorders diagnoses,
- chromosomal karyotyping and
- tumor cell identification.

From the above quoted passage, it is clear that nucleic acid detection and chromosomal karyotyping are disclosed uses for Applicants' probes.

The '069 specification is also plain in its disclosure that Applicants' self-signaling molecules are useful in nucleic acid hybridization detection and particularly in other forms of nucleic acid detection. On page 84, second paragraph, it is disclosed:

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[2] Similarly, in the context of a biotin system at page 29 in the originally filed application, Applicants make clear that the "procedures used for gene mapping (cytogenetics), and recombinant DNA-technologies" "can be equally well applied to the detection of nucleic acid sequences of bacteria, viral, fungal or parasite origin in clinical samples and this forms the basis of a powerful new approach to clinical diagnostics which does not rely on the use of radioisotopes."

> This type of ***self-signaling molecule*** can be ***used to monitor any nucleic acid hybridization reaction***. It is particularly important for ***detecting nucleic acids in gels*** (for example, ***sequencing gels***). **[emphasis added]**

Again, the passage just-quoted establishes nucleic acid hybridization reactions, nucleic acid sequencing (in sequencing gels) and nucleic acid detection gels as disclosed uses for Applicants' self-signaling molecules and probes. Such equivalent uses have already been extended in the '069 specification to nucleic acid detection, antibiotic resistance screening, genetic disorders diagnoses, chromosomal karyotyping and tumor cell identification. Thus the fact that Applicants' probes can be used with different fluorscent labels in the context of a sequencing gel is manifest from the fact that (1) different fluorescent labels are employed specifically in the context of karyotyping; (2) multiple places in the specification make it clear that the technique employed in karyotyping is equally well applied to the detection of nucleic acid sequences and (3) sequencing is a form of nucleic acid detection. This demonstrates reasonable conveyance.

The use of different colored fluorescent labels and different colored labels in nucleic acid sequencing would have been reasonably conveyed from their disclosed use in chromosomal karyotyping.

In Example 9, the '069 specification explicitly discloses labeling nucleic acids with different colored fluorescent labels and different colored labels. The text of Example 9 is partially reproduced below:

> I. **Karyotyping**
> . . . By allowing ***one set of labeled clones*** to hybridize to the chromosomes and then ***adding a fluorescent stain to the label***, the set of clones and their locations can be visualized and will ***flouresce with a particular color***. A ***second set of labeled clones*** could then be used and reacted with a ***second fluorescent dye***. The ***same process can be repeated a number of times***. Thus ***one can, if desired, have several sets of fluorescent labels attached to the cellular DNA at different but specific locations on each of the chromosomes***. These labels could be used for ***visual or computerized automatic karyotyping***.
>
> II. **Diagnosis of Genetic Disorders**
> . . . ***If necessary, two sets of labels can be used***–one which would be specific for chromosome 23 and one for some other chromosome. ***By measuring in each cell***

the ratio of the two labels, which might be of different colors, it is possible to identify the cells which show an abnormal number of chromosomes number 23. This procedure could be ***used either on slides with low-light-level video system or in a flow cytometer system using laser excitation.*** It can be ***used to determine any abnormal chromosome number.***

III. **Microorganism Detection and Identification**

The labeling of specific sequences of DNA as described above permits identification and counting of individual bacteria. In order to ***identify the individual bacteria*** to which a particular fragment of DNA hybridizes the sensitivity must be such that a single labelled structure can be detected. This can be done ***using a low-light-level video system and computer summation of images, or by using some other device for intensifying the light image.*** A flow system can also be used if the sensitivity can be made sufficiently grand. If one immobilized the bacteria on a slide their location could be found and the ***number of such fluorescent spots counted.*** This would ***provide a count of all of those bacteria which contain DNA which can hybridize whith(with) the specific clone utilized. If the clone is selected as being specific for a particular strain or bacteria, then one can count the number of organisms of that strain.*** In addition, ***any antibiotic resistance for which a particular gene has been identified could be characterized in a similar way using, as a probe,*** the DNA sequence which is contained in the antibiotic resistance gene. In addition, a ***probe could be used which is specific for a resistance plasmid containing one or more antibiotic resistance genes.*** In addition to individual bacteria, ***groups of bacterial cells of a particular strain can be detected*** and their number estimated if they are located in a small spot so that the total fluorescence specific to the hybridized DNA in the spot can be measured. In this way the ***number of organisms containing a specific DNA sequence can be measured in a mixture of bacteria.*** **[emphasis added]**

Example 9 just-quoted is telling in its disclosure. What does it tell us? First, Part I describes the use in chromosomal karyotyping of several sets of colored fluorescent labels, and that these labels can be of different colors. Second, Part II describes the use of two sets of labels which might be of different colors in order to diagnose genetic disorders. Third, using the labeling described previously for karyotyping and genetic disorder diagnoses, the third part in Example 9 conveys that the same labeling permits identfication and counting of individual bacteria. But more than that, the third part also conveys that particular strain or bacteria can be counted and that groups of bacterial cells of a particular strain can be detected. Further, any antibiotic resistance in a particular gene can

be characterized using Applicants' probes.[3] In each of the three parts of Example 9, the reader is informed that all of these labels and procedures can be carried out visually or by some automated system, be it for karyotyping, genetic disorder diagnosis or nucleic acid detection in microorganisms. And the unifying umbrella for Example 9 is its title: "Uses of Labeled DNA Sequences," and such uses include nucleic acid sequencing in sequencing gels which is another form of nucleic acid detection and identification.

In view of the foregoing remarks and above-quoted portions from the '069 specification, Applicants respectfully request that the new matter rejection of claims 1723-1724, 1740-1741, 1769-1773, 1775-1776 & 1796 be reconsidered and withdrawn.

C. Rejection Under 35 U.S.C. §112, Second Paragraph (Vagueness/Indefiniteness)

Claims 1436-1439 & 1441-1444 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. The text of the indefiniteness rejection is set forth on pages 7-8 in the May 25, 2005 Office Action.

As described above, claims 1436-1439 and 1441-1442 have been amended in light of the June 29, 2005 interview. As amended, claim 1436 now recites "[t]he process according to claim 1432, wherein said ***operator sequence is attached via a covalent attachment by an olefinic bond*** at the α-position relative to the point of attachment to said nucleotide structure or nucleotide analog structure (i) , a CH_2NH— moiety, or both." In other claims, 1437-1439 and 1441-1442, the phrase "in said nucleotide structure or nucleotide analog structure (i)" has been deleted.

It is believed that the above amendments to claims 1436-1439 and 1441-1442 obviates the indefiniteness rejection by restoring a clear antecedent basis to the claim language. In view of these claim amendments, reconsideration and withdrawal of the rejection under §112, second paragraph, is respectfully requested.

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[3] Thus, if the goal of nucleic acid detection and identfication is to distinguish different strains of bacteria, or different genes for antibiotic resistance, as set forth in Part III of Example, the use of different colored fluorescent labels and different colored labels to do so would have been reasonably conveyed to a person skilled in the art from reading Parts I and II in Example 9.

D. June 7, 2005 Miscellaneous Office Communication (Interference Request)

Applicants acknowledge with appreciation is made of the Miscellaneous Office Communication mailed on June 7, 1995, in which the Examiner indicated that Applicants' Request for Interference filed on September 28, 2004 is being held in abeyance at this time due to awaiting compliance with 37 CFR 41.102 regarding completion of examination. It is believed that the claim cancellations effected by this paper and the other claim amendments, together with Applicants' response to the outstanding issues in the May 25, 2005 Office Action, places all of the now pending claims in allowable condition so that the interference can proceed.

An early indication both as to the allowability of the pending claims and suspension of *ex parte* prosecution pending resolution of the interference is respectfully requested.

Early and favorable action is respectfully requested.

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SUMMARY AND CONCLUSIONS

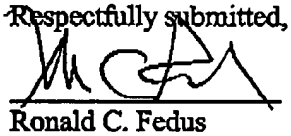
In light of the above claim cancellations, Applicants believe that no additional fees are due in connection with this paper. No new claims have been added and in light of the cancellation of four claims, the total number of claims pending in this application is less than the number of previously paid for claims. In the event that any additional fees are due, however, Applicants hereby requests that the Patent and Trademark Office charge the amount of any such fees to Deposit Account No. 05-1135.

Early and favorable action is respectfully requested.

If a telephone conversation would further prosecution of the application, the Examiner is welcome to call Applicant's undersigned attorney at the number below.

July 7, 2005

Respectfully submitted,



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